

Application No. 10/555,039
Amendment dated June 29, 2009
After Final Office Action of January 5, 2009

Docket No.: 03702/0203547-US0

AMENDMENTS TO THE SPECIFICATION

Please delete the paragraph beginning at page 3, line 20 and ending at page 4, line 10 of the original specification, and insert therefor the following substitute paragraph:

The present invention includes,

- (1) a crystal of Compound B, which has diffraction peaks at least at 7.3°, 14.7°, 19.2° and 22.3° in the powder X-ray diffraction spectrum;
- (2) a method for producing a crystal of Compound B, which comprises performing crystallization from an acetonitrile solution of Compound A by controlling its supersaturation concentration (g/100 g) to be from 2.15 to 2.36 at the time of occurrence of spontaneous ~~nucleus~~ nucleation;
- (3) a method for producing a crystal of Compound B, which comprises performing crystallization from an acetonitrile solution of Compound A by controlling its supersaturation concentration (g/100 g) to be from 0.41 to 2.36 at the time of addition of a seed crystal; and
- (4) the production method described in (3), wherein the solution at the time of addition of the seed crystal has a temperature of 70°C or lower.

Please delete the paragraph beginning at page 4, line 11 and ending at page 4, line 13 of the original specification, and insert therefor the following substitute paragraph:

In the present invention, the term “spontaneous ~~nucleus~~ nucleation” means crystal nucleus which occurs spontaneously when performing crystallization without using seed crystal.

Please delete the paragraph beginning at page 4, line 22 and ending at page 4, line 25 of the original specification, and insert therefor the following substitute paragraph:

Cs (g/100 g) indicates the saturation solubility (in terms of the desolvate) of Compound B dissolved in 100 g of a solvent under the temperature at the time of occurrence of spontaneous ~~nucleus~~ nucleation or addition of seed crystal.

Please delete the paragraph beginning at page 6, line 10 and ending at page 6, line 15 of the original specification, and insert therefor the following substitute paragraph:

A crystal of Compound B can be produced by setting the supersaturation concentration (g/100 g) at the time of occurrence of spontaneous ~~nucleus~~ nucleation to be from 2.15 to 2.36, and performing crystallization from an acetonitrile solution of Compound A while suppressing formation of the type I or type II crystal of Compound A.

Please delete the paragraph beginning at page 6, line 16 and ending at page 7, line 8 of the original specification, and insert therefor the following substitute paragraph:

On the other hand, in the case where crystallization is performed under the condition of adding seed crystals, obtained crystals depends on the crystal form of the seed crystal. Therefore, the crystal of Compound B can be produced even under the condition where the supersaturation concentration (g/100 g) is from 0.41 to 2.36 in the crystallization by adding seed crystals compared with the crystallization by occurrence of spontaneous ~~nucleus~~ nucleation. It is preferred that seed crystals are added in an amount larger (not less than 0.004 g/100 g of solvent) than usual (less than 0.004 g/100 g of solvent). In the case where the amount of seed crystals is small, the added seed crystals become a stimulus and occurrence of new spontaneous ~~nucleus~~ nucleation is observed. However, in the case where the seed crystals are added in a large amount, growth of the added seed crystal takes

priority, and occurrence of spontaneous ~~nucleus~~ nucleation is suppressed, whereby contamination of the type I or type II crystal of Compound A can be suppressed to the minimum level.

Please delete the paragraph beginning at page 7, line 9 and ending at page 7, line 14 of the original specification, and insert therefor the following substitute paragraph:

The crystal of Compound B is subjected to solvent mediated transformation, therefore, the temperature of a solution at the time of occurrence of spontaneous ~~nucleus~~ nucleation and at the time of addition of seed crystals is controlled to be 70°C or lower, preferably 67°C or lower, and more preferably 55°C or lower.

Please delete Table 1, which appears on page 17, lines 1-26 of the original specification, and insert therefor the following:

Table 1

Feed concentration (C)	Seed crystal	Temperature at the time of occurrence of spontaneous nucleus <u>nucleation</u> or addition of seed crystals (°C)	Solubility at the time of occurrence of spontaneous nucleus <u>nucleation</u> or addition of seed crystals (Cs)	Supersaturation concentration (Cx)	Precipitated crystal form
2.14	Non	25	0.29	1.85	B+I
2.44	Non	25	0.29	2.15	B
2.40	Non	17	0.19	2.21	B
2.40	Non	14.3	0.16	2.24	B
2.68	Non	27	0.32	2.36	B
3.66	Non	0	0.07	3.59	II
2.32	III	50	1.00	1.32	B+I
1.80	III	25	0.29	1.51	B+I
1.89	III	25	0.29	1.60	B
2.00	III	25	0.29	1.71	B
2.14	III	25	0.29	1.85	B
2.21	III	25	0.29	1.92	B
2.39	III	30	0.38	2.01	B
2.41	III	25	0.29	2.12	B

2.68	III	25	0.29	2.39	B
2.73	III	25	0.29	2.44	B
2.36	B	70	2.36	0.00	B+I
0.70	B	25	0.29	0.41	B
2.36	B	65	1.92	0.44	B
1.34	B	45	0.79	0.55	B
1.07	B	30	0.38	0.69	B
1.61	B	45	0.79	0.82	B
1.25	B	25	0.29	0.96	B
1.43	B	30	0.38	1.05	B
2.36	B	55	1.25	1.11	B
1.52	B	25	0.29	1.23	B
1.75	B	30	0.38	1.37	B
1.75	B	25	0.29	1.46	B
2.36	B	45	0.79	1.57	B
1.96	B	25	0.29	1.67	B
2.10	B	30	0.38	1.72	B
2.14	B	25	0.29	1.85	B
2.36	B	30	0.38	1.98	B
2.36	B	25	0.29	2.07	B
2.41	B	25	0.29	2.12	B

Please delete the paragraph beginning at page 18, line 13 and ending at page 18, line 21 of the original specification, and insert therefor the following substitute paragraph:

In addition, in the case where seed crystals were not added, the crystal of Compound B was obtained when the supersaturation concentration (g/100 g) at the time of occurrence of spontaneous ~~nucleus~~ nucleation was from 2.15 to 2.36. However, when the supersaturation concentration was higher than the range, contamination of the type II crystal of Compound A was observed, and when it was lower than the range, contamination of the type I crystal of Compound A was observed.